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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/530,061	Notomi et al.
Examiner	**Group Art Unit**
Arun Chakrabarti	1655

☒ *Responsive to communication(s) filed on* Sep 1, 2000 .

☐ *This action is* **FINAL.**

☐ *Since this application is in condition for allowance except for formal matters,* **prosecution as to the merits is closed** *in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

A shortened statutory period for response to this action is set to expire 3 *month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).*

Disposition of Claims

☒ *Claim(s)* 1-11 and 13-28 *is/are pending in the application.*

Of the above, claim(s) _____ *is/are withdrawn from consideration.*

☐ *Claim(s)* _____ *is/are allowed.*

☒ *Claim(s)* 1-11 and 13-28 *is/are rejected.*

☐ *Claim(s)* _____ *is/are objected to.*

☐ *Claims* _____ *are subject to restriction or election requirement.*

Application Papers

☐ *See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.*

☐ *The drawing(s) filed on* _____ *is/are objected to by the Examiner.*

☐ *The proposed drawing correction, filed on* _____ *is* ☐*approved* ☐*disapproved.*

☐ *The specification is objected to by the Examiner.*

☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

☒ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

☒ *All* ☐ *Some** ☐ *None of the CERTIFIED copies of the priority documents have been*

☒ *received.*

☐ *received in Application No. (Series Code/Serial Number)* _____ .

☐ *received in this national stage application from the International Bureau (PCT Rule 17.2(a)).*

**Certified copies not received:* _____ .

☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

☒ *Notice of References Cited, PTO-892*

☐ *Information Disclosure Statement(s), PTO-1449, Paper No(s).* _____

☐ *Interview Summary, PTO-413*

☐ *Notice of Draftsperson's Patent Drawing Review, PTO-948*

☐ *Notice of Informal Patent Application, PTO-152*

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-20 and 25-28 are rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 1, the preamble of the instantly claimed method is drawn to a method for synthesizing nucleic acid while the final process step is that of displacing the complementary chain and it is thus unclear as to whether the instantly claimed method is drawn to a method for synthesizing nucleic acid or rather displacing the complementary chain. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble.

Similarly, for the method of claim 9, the preamble of the instantly claimed method is drawn to a method for amplifying nucleic acid while the final process step is that of making ready of the chain with the 3'-terminal for base pairing and it is thus unclear as to whether the instantly claimed method is drawn to a method for amplifying nucleic acid or rather making ready of the chain with the 3'-terminal for base pairing. Method claim requires a last step or

phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble

Claims 1 and 9 lack such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

Claims 1-20 and 25-28 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected over the recitation of the phrase, "giving nucleic acid". It is not clear who is giving the nucleic acid and where it is being given. It is also not clear who is receiving the nucleic acid and where it is being received. Is the natural nucleic acid being donated by somebody or being artificially synthesized? The metes and bounds of the claim is vague and indefinite.

Claims 1 and 9 are also rejected over the recitation of the phrase, "capable of". Regarding claims 1 and 9, the phrase "capable of" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 3, 4 and 5 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear whether the limitations following the colons after X2, X1c , F2, F1c, R2 and R1c are additional part of the claimed invention or merely the definitions of the regions are cited in the claimed invention. Even if it is considered as definitions of the terms, it is unclear how the same terms are used in a statement to define that particular term, e.g., the term "a region X1c" is used to define the same. The metes and bounds of the claims are vague and indefinite.

Claims 3-5 are also rejected over the recitation of the phrase, "substantially". It is unclear how much similarity in nucleotide sequence is claimed in the invention. Is the absolute similarity (100 %) claimed or 50-99% similarity is claimed. The metes and bounds of the claims are vague and indefinite.

Claim 18 is rejected over the recitation of the phrase, "labeled on particles". It is unclear what particles are claimed in the invention. Is the nucleic acid particles are claimed or the particles of a solid support are claimed or both are claimed? The metes and bounds of the claims are vague and indefinite.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

4. Claims 1-6, 8-11, 16-20 and 25 are rejected under 35 U.S.C. 102 (e) as being anticipated by Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999).

Cleuziat et al teach a method of synthesizing nucleic acid having complementary nucleotides sequences linked alternately in a single-stranded chain (Figure 4B), comprising :

a) the step of providing nucleic acid at the 3'-terminal thereof with a region F1 capable of annealing to a part F1c in the same chain and which upon annealing of the region F1 to F1c, is capable of forming a loop containing a region F2c capable of base pairing (Example 4, Figures 1-4),

b) the step of performing synthesis of a complementary chain wherein the 3'-terminal of F1 having annealed to F1c serves as the origin of synthesis (region F1 capable of annealing to a part F1c in the same chain and which upon annealing of the region F1 to F1c, is capable of forming a loop containing a region F2c capable of base pairing (Figures 2-4),

c) the step of annealing, to a region F2c, of an oligonucleotide provided with the 3'-terminal thereof with F2 consisting of a sequence complementary to the region F2C, followed by synthesis, with the oligonucleotide as the origin of synthesis, of a complementary chain by a polymerase catalyzing the strand displacement reaction of synthesizing a complementary chain to

displace the complementary chain synthesized in step b) (Example 4, column 24, lines 26-42 and Figure 4B), and

d) the step of annealing, to the complementary chain displaced in step c) to be ready for base pairing, of a polynucleotide provided at the 3'-terminal thereof with a sequence complementary to an arbitrary region in the chain synthesized in step c), followed by synthesis, with the 3'-terminal as the origin of synthesis, of a complementary chain by a polymerase catalyzing the strand displacement reaction of synthesizing a complementary chain to displace the complementary chain synthesized in step c) (Figure 4B).

Cleuziat et al teach a method wherein in step d), the origin of synthesis is a region R1 present at the 3'-terminal in the same chain and capable of annealing to a region R1c, and a loop containing the region R2c capable of base pairing is formed by annealing R1 to R1c (Figures 1-4).

Cleuziat et al inherently teach an oligonucleotide comprising at least two regions X2 and X1c, and X1c is linked to the 5'-side of X2, whereas X2 is a region having a nucleotide sequence complementary to an arbitrary region X2c in nucleic acid having a specific nucleotide sequence (a and a' regions in Figure 1), and

X1c is a region located at the 5'-side of the region X2c in nucleic acid having a specific nucleotide sequence (e region in Figure 1).

Cleuziat et al teach a method, wherein the nucleic acid in step a) is second nucleic acid provided by the following steps:

I) the step of annealing, to a region F2c in nucleic acid serving as a template, of a region F2 in an oligonucleotide comprising at least two regions F2 and F1c, and F1c is linked to the 5'-side of F2, whereas F2 is a region having a nucleotide sequence complementary to an arbitrary region F2c in nucleic acid having a specific nucleotide sequence (a and a' regions in Figure 1 and column 16, lines 3-50), and

F1c is a region located at the 5'-side of the region F2c in nucleic acid having a specific nucleotide sequence (e region in Figure 1 and column 16, lines 3-50).

ii) the step of synthesizing first nucleic acid having a nucleotide sequence complementary to the template wherein F2 in the oligonucleotide serves as the origin of synthesis (Figure 4B).

iii) the step of rendering an arbitrary region in the first nucleic acid synthesized in step ii) ready for base pairing (Figure 4B), and

iv) the step of annealing an oligonucleotide having a nucleotide sequence complementary to the region made ready for base pairing in the first nucleic acid in step iii), followed by synthesizing second nucleic acid with the oligonucleotide as the origin of synthesis and rendering F1 at the 3'-terminal thereof ready for base pairing (Figure 4B).

Cleuziat et al inherently teach an oligonucleotide comprising at least two regions R2 and R1c, and R1c is linked to the 5'-side of R2, whereas R2 is a region having a nucleotide sequence complementary to an arbitrary region R2c in nucleic acid having a specific nucleotide sequence (a and a' regions in Figure 1 and column 16, lines 3-50), and

R1c is a region located at the 5'-side of the region R2c in nucleic acid having a specific nucleotide sequence (e region in Figure 1 and column 16, lines 3-50).

Cleuziat et al teach the method wherein the step of rendering base pairing ready in steps iii) and iv) is conducted by the strand displacement synthesis of complementary chain by a polymerase catalyzing the strand displacement reaction of synthesizing complementary chain (Examples 4 and 5 and Figure 4B).

Cleuziat et al teach the method wherein the nucleic acid serving as the template is RNA, and the synthesis of complementary chain is conducted by an enzyme having a reverse transcriptase activity (Figure 9 and Example 5, column 26, lines 27-32).

Cleuziat et al teach the method of amplifying nucleic acid (Example 9 and Figure 9) having complementary nucleotide sequences linked alternately in a single stranded chain by repeatedly conducting the following steps a) the step of providing nucleic acid at the 3'-terminal thereof with a region F1 capable of annealing to a part F1c in the same chain and which upon annealing of the region F1 to F1c, is capable of forming a loop containing a region F2c capable of base pairing (Example 4, Figures 1-4 and column 16, lines 3-50),

b) the step of performing synthesis of a complementary chain wherein the 3'-terminal of F1 having annealed to F1c serves as the origin of synthesis (region F1 capable of annealing to a part F1c in the same chain and which upon annealing of the region F1 to F1c, is capable of forming a loop containing a region F2c capable of base pairing (Figures 2-4),

c) the step of annealing, to a region F2c, of an oligonucleotide provided with the 3'-terminal thereof with F2 consisting of a sequence complementary to the region F2C, followed by synthesis, with the oligonucleotide as the origin of synthesis, of a complementary chain by a polymerase catalyzing the strand displacement reaction of synthesizing a complementary chain to displace the complementary chain synthesized in step b) (Example 4, column 24, lines 26-42 and Figure 4B), and

d) the step wherein the chain with the 3'-terminal made ready for base pairing in step c) serves as a new template (Example 9 and Figure 9)

Cleuziat et al teach the method of detecting a target nucleotide sequence in a sample, which comprises performing an amplification method and observing whether an amplification reaction product is generated or not (Example 9 and Figure 9 and Example 10 and Figure 10).

Cleuziat et al teach the method wherein a probe containing a nucleotide sequence complementary to the loop is added to the amplification reaction product and hybridization therebetween is observed (Example 10, Column 32, lines 2-5).

Cleuziat et al teach the method wherein the probe is labeled and aggregation reaction occurring upon hybridization is observed (Example 11).

Cleuziat et al teach the method of detecting a mutation in a target nucleotide sequence by the detection method, wherein a mutation in a nucleotide sequence as the subject of amplification prevents synthesis of any one of complementary chains constituting the amplification method (Example 9, Column 31, lines 4-25).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-11, 16-20 and 25 are rejected under 35 U.S.C. 103(a) over Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999).

Cleuziat et al teach the method and oligonucleotides of claims 1-6, 8-11, 16-20 and 25 as described above.

Cleuziat et al do not teach the method wherein the melting temperature of outer primer or region at the 3'-side in the template is less or equal than the melting temperature of (F2c/F2 and R2c/R2) which in turn is less or equal than the melting temperature of (F1c/F1 and R1c/R1).

However, it is *prima facie* obvious that selection of the melting temperature of a particular oligonucleotide represents routine optimization with regard to the G-C and A-T content which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the oligonucleotide melting temperature selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

7. Claims 1-11, 13-20 and 25-28 are rejected under 35 U.S.C. 103 (a) over Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999) in view of Yager et al. (U.S. Patent 6,025,139) (February 15, 2000).

Cleuziat et al. teach the method and oligonucleotides of claims 1-11, 16-20 and 25 as described above.

Cleuziat et al do not teach the method wherein the nucleotide synthesis is carried out in the presence of a melting temperature regulator betaine at a concentration of 0.2 to 3.0M.

Yager et al teach the method wherein the nucleotide synthesis is carried out in the presence of a melting temperature regulator betaine at a concentration of 5M (Column 7, lines 49-52).

However, it is *prima facie* obvious that selection of the concentration of melting temperature regulator betaine represents routine optimization with regard to the G-C and A-T content of a particular nucleotide used in the amplification and hybridization reaction which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the concentration of melting temperature regulator betaine selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the melting temperature regulator betaine of Yager et al. in the method of strand displacement amplification reaction of Cleuziat et al. since Yager states, "Alternatively, an isostabilizing solvent, such as 5M betaine, could be used to eliminate the differences in melting temperature between A:T and G:C base pairs (column 7,

lines 49-52)." An ordinary practitioner would have been motivated to combine and substitute the melting temperature regulator betaine of Yager et al. in the method of strand displacement amplification reaction of Cleuziat et al. , in order to achieve the express advantage, as noted by Yager et al, of an isostabilizing solvent betaine which could be used to eliminate the differences in melting temperature between A:T and G:C base pairs.

8. Claims 1-11 and 13-28 are rejected under 35 U.S.C. 103 (a) over Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999) in view of Yager et al. (U.S. Patent 6,025,139) (February 15, 2000) further in view of Stratagene Catalog (1988, Page 39).

Cleuziat et al. in view of Yager et al expressly teach the method claims and assay reagents of 1-11, 13-20 and 25-28 as described above in detail.

Cleuziat et al. in view of Yager et al. does not teach the motivation to combine all the reagents for synthesizing a nucleic acid in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a suitable container and all the reagents as taught by Cleuziat et al. in view of Yager et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a

series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control " (Page 39, Column 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph. D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Kr. Chakrabarti

Arun Chakrabarti,

Patent Examiner

January 19, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER